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PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Application Number	Filed
09/896,812	June 29, 2001
First Name Inventor: Thomas D. Madden	
Art Unit: 1615	Examiner: Gollamudi S. Kishore

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96.)
- ☒ attorney or agent of record. Registration No. 51,909
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____.

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February 1, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

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PRE-APPEAL BRIEF REQUEST FOR REVIEW REMARKS

The instant application is directed, in part, to novel liposomal drug formulations containing precipitated drug within the liposome. This invention is based upon the surprising discovery by Applicants that, at relatively high drug:lipid ratios, precipitation of a drug within a liposome leads to increased drug retention within the liposome *in vivo*. This contravenes the previous understanding in the art, which was that higher drug:lipid ratios lead to increased drug leakage from liposomes. Increased drug retention is desirable, since this correlates with a greater amount of drug remaining in the liposome when it reaches its target site, *e.g.*, tumor, within a patient's body. The present invention, drawn to liposomal drug formulations wherein a substantial portion of liposome-encapsulated drug is precipitated, provides for liposomal drug formulations having two advantageous properties previously thought to be incompatible: (1) high drug:lipid ratio; and (2) increased drug retention.

Pending claims 36, 43, and 66-68 are drawn to one very specific embodiment of the present invention, which is a liposomal formulation of the anti-neoplastic drug, vinorelbine. The claimed formulation has the relatively high drug:lipid ratio of 0.1-0.5:1 (w/w), and at least 50% of the liposome-encapsulated vinorelbine is precipitated. In addition, the liposomes comprise sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% to 30/50 mol%/mol% sphingomyelin/cholesterol. As shown in Figure 1 of the instant application, as the vinorelbine:lipid ratio increases from 0.1:1 to 0.2:1 to 0.3:1 (w/w), there is a corresponding increase in vinorelbine retention, which is a consequence of vinorelbine precipitation within the liposomal interior.

The pending claims stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,110,491 ("Kirpotin") in combination with U.S. Patent No. 5,543,152 ("Webb"). According to the Examiner, Kirpotin discloses liposomal compositions wherein the active agent is in a precipitated form; the active agent can be any compound with an ionizable group, including antineoplastic agents such as doxorubicin, vincristine, vinblastine, and vinorelbine; and the liposomes may be made from any of a variety of various phospholipids and sphingomyelin, and may include cholesterol. The Examiner further asserts that the drug:lipid ratio of the liposomal doxorubicin formulations described in Kirpotin

appears to fall within the claimed ratios. The Examiner observes that Kirpotin exemplifies only liposomes made from phosphatidylcholine and cholesterol, and not sphingomyelin, but concludes that it would have been obvious to use sphingomyelin instead of phospholipid in the liposomes, since Kirpotin is suggestive of the use of sphingomyelin, and Webb teaches several advantages of using sphingomyelin and cholesterol.

Applicants respectfully submit that the Examiner has clearly failed to establish a *prima facie* case of obviousness, since he has failed to establish at least two elements essential for a *prima facie* case. First, he has failed to demonstrate that the prior art references relied upon teach each and every element of the claimed liposomal formulations. Second, he has failed to establish that the skilled artisan would be motivated to select various features generally described in the prior art references to achieve the specific liposomal vinorelbine formulation recited in the instant claims. Accordingly, the rejection under Section 103 over the combination of Kirpotin and Webb is clearly improper and without factual or legal basis. Specific comments directed to each of these deficiencies in the *prima facie* case of obviousness are provided in turn below.

(1) *Prior Art References Do Not Teach or Suggest All Claim Limitations*

The Examiner has failed to establish that the prior art references describe each element of the claimed liposomal formulation. The pending claims are directed to a very specific liposomal vinorelbine formulation, wherein the liposome components, the drug, and the drug:lipid ratio are specified, based upon Applicants' discovery of a specific liposomal vinorelbine formulation having superior pharmacokinetic properties, including slower drug release. Applicants submit that the Examiner has failed to identify where either Kirpotin or Webb describe a liposomal vinorelbine formulation having a vinorelbine to lipid ratio of 0.1-0.5:1 (w/w). Applicants further submit that neither of these references teach or suggest a liposomal vinorelbine formulation having this feature.

Webb fails to describe vinorelbine at all, and, when describing liposomal formulations comprising vincristine (another vinca alkaloid), Webb indicates that vincristine may be present at a drug:lipid ratio in the range of approximately 0.01-0.2:1 (w/w) (column 2, lines 42-44, and column 3, lines 21-23). This range is substantially different than the presently claimed range of 0.1-0.5:1 (w/w). Furthermore, it is clear that it is not mere oversight that leads

Webb to describe such a low and narrow drug:lipid ratio for vincristine, since the drug:lipid ratio that Webb describes for swainsonine is 0.01-0.5:1 (mol/mol), which is a much broader range. Thus, Webb clearly fails to teach liposomal vinorelbine at a ratio of 0.1-0.5:1 (w/w). Rather, the conclusion to be drawn from Webb appears to be that different drugs will have different preferred drug:lipid ratios.

Kirpotin, on the other hand, specifically recites vinorelbine in a long list of ionizable compounds that might be used in certain liposomal formulations described therein (column 6, line 18). However, regarding vinorelbine:lipid ratios, Kirpotin is completely silent. The only drug:lipid ratios described in Kirpotin are for the compound doxorubicin. For this drug, Kirpotin recites various doxorubicin:lipid ratios that result from loading liposomes containing different internal salts. There appears to be a wide range of resulting doxorubicin:lipid ratios, *e.g.*, from .008-.246:1 (mol/mol). Kirpotin does not provide a drug:lipid ratio for vinorelbine, and clearly does not describe the vinorelbine:lipid range of 0.1-0.5:1 (w/w) recited in the instant claims. The Examiner asserts that Kirpotin recites a drug:lipid ratio that falls within the claimed ratio. Even assuming *arguendo* that this is true, the recitation of one or more different doxorubicin:lipid ratios clearly does not amount to a description of a vinorelbine:lipid ratio of 0.1-0.5:1 (w/w), and cannot render the claimed liposomal formulation obvious.

As described in the instant specification and understood in the art, not all lipid formulations are equal for drug delivery purposes, and the optimal drug:lipid ratio varies for different drugs. Thus, extensive research continues in an effort to identify formulations that demonstrate preferred characteristics for drug loading and storage, drug administration, pharmacokinetics, biodistribution, leakage rates, tumor accumulation, toxicity, and other features (paragraph 6). Accordingly, the identification and selection of a preferred liposomal drug formulation with advantageous properties requires considerable effort and experimentation, and the resulting formulation is not obvious in light of a reference that fails to identify the specific features of a preferred liposomal formulation of a particular drug, *e.g.*, vinorelbine.

In addition, the skilled artisan would appreciate that the specific liposome components (*e.g.*, lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties

of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.*, solubility, half-life, and size) will contribute to determining the best combination of these features. Thus, the identification of a specific combination of lipid components and drug:lipid ratio for a particular drug, which provides superior pharmacokinetic properties for that drug, requires more than merely routine experimentation.

In light of the comments provided above, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness of the pending claims over Kirpotin and Webb, since neither of these references teach or suggest a liposomal vinorelbine formulation having a vinorelbine:lipid ratio of 0.1-0.5:1 (w/w). This feature is not described in either reference, and would clearly not be considered common knowledge in the art. It is well established that all claim limitations must be taught or suggested by the prior art, in order to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981 (CCPA 1974).

(2) *No Motivation to Combine Prior Art References*

The Examiner has clearly failed to establish that the skilled artisan would be motivated by the prior art references and knowledge in the art to achieve the specifically claimed liposomal vinorelbine formulation. The Examiner broadly asserts that the skilled artisan would be motivated to substitute sphingomyelin for phosphatidylcholine, since Webb teaches advantages of using sphingomyelin. However, the Examiner does not provide any statement indicating where motivation to use vinorelbine at the claimed drug:lipid ratio of 0.1-0.5:1 (w/w) is provided. Furthermore, the Examiner fails to provide any motivation as to why the skilled artisan would select this drug:lipid ratio when using sphingomyelin instead of phosphatidylcholine. It is well established that if obviousness is found by combining multiple references, there must also be some motivation to combine the prior art teachings in the particular manner claimed. *See, e.g., In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000) "Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." 217 F.3d at 1371. In the present case, the Examiner has presented absolutely no motivational

basis for the skilled artisan to use the specifically claimed combination of the drug vinorelbine in a sphingomyelin and cholesterol-based liposome, at a drug:lipid ratio of 0.1-0.5:1 (w/w).

In addition, Applicants submit that the cited prior art references and knowledge in the art fail to provide any motivation to combine various features of the claimed invention. As discussed above, the optimal drug:lipid ratio varies for different drugs. The specific liposome components (*e.g.,* lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.,* solubility, half-life, and size) will contribute to determining the best combination of these features. Accordingly, the identification and selection of a preferred liposomal formulation for any particular drug requires considerable effort and experimentation and cannot be readily predicted by analogy to other drugs or formulations. Neither Kirpotin nor Webb provide any motivation to combine all of the features recited in the pending claims, including: (1) the specified drug (vinorelbine); (2) the specified liposome (comprising 75/25-30/50 mol%/mol% sphingomyelin/cholesterol); and (3) the specified drug:lipid ratio (0.1-0.5:1 (w/w)), to achieve the specifically claimed liposomal vinorelbine formulations. Neither reference provides any teaching or suggestion to use vinorelbine at the claimed drug:lipid ratio, or any teaching or suggestion to produce liposomal formulations having the particular combination of claimed features. Applicants can only conclude that the Examiner is applying impermissible hindsight, based upon the teachings of the instant application, in drawing his conclusion that the presently claimed invention is obvious over Kirpotin and Webb.

Respectfully submitted,

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